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(54) Use of phytic acid or its salts for the treatment of hyperlipemia, obesity and obesity-related diseases.

(57) Phytic acid or a salt thereof is known for pharmaceutical use: they are now administered orally as a treatment or preventive of hyperlipemia, obesity and obesity-related diseases. Suitable non-toxic salts are metal salts and salts of an organic base, a base amino acid or an organic ester residue.

The phytic acid or salt may be contained in a foodstuff, confectionary or a liquid or pharmaceutical type of composition. A daily dose of 1-100 mg per kg body weight is suitable.

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Description

USE OF PHYTIC ACID OR ITS SALTS FOR THE TREATMENT OF HYPERLIPEMIA, OBESITY AND OBESITY-RELATED DISEASES

The present invention relates to the use of a pharmaceutical composition for oral administration containing phytic acid or salts thereof which is especially used for the treatment of hyperlipemia, obesity and obesity-related diseases.

Hyperlipemia refers to diseases caused by abnormal increases in one or more serum lipids viz., cholesterol triglyceride, phospholipid and free fatty acids and is accompanied by various disorders.

These diseases are generally classified as Type IV induced by the cumulation of endogenous triglyceride, Type 1 induced by the cumulation of exogenous triglyceride, and a Type V which is induced by a combination of these causes.

Heretofore, various pharmaceutical compounds have been known for treating hyperlipemia. For instance, preparations based on clofibrate, dextran sulfate and nicotinic acid have been known for Type IV hyperlipemia and hormone preparations such as progesterone and nicotinic acid for Type V. However, although it has been reported that some amylase inhibitors are effective for Type 1, no substantially effective pharmaceutical compounds havebeen reported.

As remedies for obesity, on the other hand, there is known one type of drug based on hormones, amino acids, inorganic substances, rutin and vitamins which are administered directly to a living body to serve to promote the metabolism and decomposition of fats, and another type of pharmaceutical compound based on Lactobacillus which serves to prevent in-vivo propagation of harmful bacteria, resulting in the intestinal absorption of nutrients such as amino acids and inorganic substances being promoted and intestinal disorders and metabolism being improved.

In expectation of an effect by restricted diets, treatments have been carried out with indigestible mannans or diet fibres which induce a feeling of fullness. However, since pharmaceuticals having a decisive remedial effect have been found to tend to be strongly poisonous, there is still a demand for pharmaceuticals administrable with high safety and great remedial effects.

Phytic acid is a compound which has been known for a long tine and is reported to promote the cultivation of Lactobacillus bacteria by phytic acid has already been found by the present inventors (Japanese Patent Application No. 63-140385).

Phytic acids widely appear in plants as calcium and magnesium salts, sometimes a potassium salt. For instance, rice bran contains as high as 9.5 to 14.5 % of phytic acid, and provides a starting material for commercial phytic acid and myoinositol derived therefrom.

Phytic acid and its salt have been used for many purposes in pharmaceutical applications, calcium phytate has been used to assist absorption of calcium, rice bran itself and sodium phytate as a preventive for calcium calculus, and potassium phytate for the treatment of hypercalcemia and hyper-calciuria of sarcoidosis patients. They have also been utilized in various other fields as fermentative aids for brewing saké and wine, metal removers making use of the chelating action of phytic acid, antioxidants in the presence of iron and calcium ions and anticorrosives for metals.

However, it has not been reported that phytic acid and its salts may be effective as a preventive and remedy for hyperlipemia, especially arteriosclerosis.

In view of the foregoing, the object of the present invention is to utilise a pharmaceutical composition effecttive for the treatment and prevention or arteriosclerosis, especially all the types of hyperlipemia, including Type I.

Another object of the present invention is to utilise a pharmaceutical composition for treating obesity and obesity-related diseases which allows patients suffering from obesity, especially functional obesity, to lower their body weight without a lowering of their function and bodily strength and are also usable even by healthy individuals.

The inventors have already discovered that when orally administered during nutrition experiments, phytic acid serves to reduce body smells, especially, bad breath, perspiratory smell and urinous smell. Further research studies of the effects of such removal has revealed that this is related to in-vivo metabolism, especially the promotion of decomposition and metabolism of fats, leading to the present invention. The present invention is characterized by the use of phytic acid or a salt thereof, for the remedy, treatment and prevention of hyperlipemia, obesity and obesity-related diseases; the latter include fatty liver, diabetes and macromastia.

The compositions used herein, and specific examples thereof may be the same as disclosed in our EPA 89302267.3 wherein phytic acid is used as an antidote to poisoning by drugs or alcohol.

The present invention will later be described with reference to the accompanying illustrative drawings, in which:-

Figure 1 is a graph ilustrating changes of free fatty acids in blood with a change in the amount of phytic acid administered, and

Figure 2 is a graph illustrating the results of induction-testing-with-time of free fatty acids after the administration of phytic acid.

As the salt of phytic acid, the most preference is given to an iron salt, due to its increased effect. The iron salt of phytic acid is easily administered by an oral route, and may be used in the form of powders or granules or mixed with food and drink by suitable means.

The phytates usable in the present invention may include non-toxic metal salts as well as non-toxic salts with organic salts, basic amino acids and organic ester residues such as, for instance, those represented by potassium phytate, sodium phytate, ammonium phytate, arginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamine phytate, triethanolamine phytate and glucamine phytate.

A suitable dosage to humans, generally adults, of the compositions of the present invention, although varying depending upon conditions and types of preparations, is 1 to 100 mg/kg a day, as calculated in terms of phytic acids.

In various preparations, phytates and their mixtures in a pH range of 6 to 8 may generally be selectively used depending upon the purposes of the pharmaceuticals as well as the functional diets because of their strong acidity.

The number of moles of various bases required to adjust one mole of phytic acid to pH 6 to 8 is shown in Table 1.

Table 1

Bases	pH: 6.00	7.00	8.00
NaOH	7.34	8.21	8.94
KOH	7.34	8.23	8.94
LiOH	7.41	8.38	9.30
NH_4OH	7.61	8.55	9.45
$HOC_2HCH_2NH_2$	7.72	8.68	9.52
$(HOCH_2CH_2)_2NH$	7.54	8.45	9.31
$(HOCH_2CH_2)_3N$	7.20	8.53	12.1
N-Methylglucamine	7.62	8.49	9.25
L-Arginine	7.79	8.67	9.60
L-Lysine	8.01	8.98	10.0
L-Histidine	11.3	-	-

Phytic acid and its salt are so tasteless and odorless that their oral administration is easily achieved. Compositions thereof may be used alone as pharmaceuticals or may be added to food and diets for increased nutrition. Thus, the pharmaceutical compositions used in the invention may be administered by mixing with drinking water for humans and animals or sprinkling over or blending with dishes or feed in the form of powders or granules.

The pharmaceutical compositions used in the present invention are effective for remedying or treating obesity and hyperlipemia, since they serve to promote the metabolism of fats, to cure coprostasis and diarrhoea and to promote the absorption of nutrients such as vitamins. These desired effects are easily obtained by oral administration.

Moreover, the compositions used are so safe that they are continuously usable and are effective for the inhibition of obesity by their continued use or administration.

The present invention will now be explained in detail with reference to the following illustrative examples.

Example 1

Composition a

Twenty-nine (29) g of sodium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition b

Four hundred and twelve (412) g of potassium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition c

One hundred and seventy-seven (177) g of lithium hydroxide and a suitable amount of refined water are

added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition d

Five hundred and eighty-one (581) g of ethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition e

Nine hundred and seventy-nine (979) g of diethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition f

One thousand eight hundred and five (1805) g of triethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition g

One thousand six hundred and fifty-seven (1657) g of N-methylglucamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition h

One thousand five hundred and ten (1510) g of L-arginine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition i

One thousand seven hundred and fifty-three (1753) g of L-histidine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition j

One hundred and sixteen (116) g of sodium hydroxide, 478 g of potassium hydroxide, 6.08 g of potassium chloride (as a dihydrate), 157 g of disodium hydrogen phosphate (as an anhydride) and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 9.

These compositions a to j may be powdered by crystallization or the addition of a vehicle.

These compositions a to j may also be formed into compositions in the form of liquids or powders, from which the preparations may be obtained.

Example 2

The composition j obtained in Example 1 was formed into the compositions below, from which various preparations were obtained.

Composition A for Preparations

Lactose is added to the composition j (containing 200 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition B for Preparations

Lactose is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition C for Preparations

Refined water is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition D

Light silicic anhydride is added to the composition j (containing 200 mg of phytic acid), followed by drying, which gives a total of 1000 mg of a composition.

Production Examples of Preparations

Production Example 1 (Elixir)

Composition C	100 g	(10 g calculated as phytic acid)
Compound orange extract	24 ml	
Ethanol	400 ml	
Glycerine	400 ml	
Refined Water	Total: 1000 ml	

Predetermined amounts of the aforesaid components are uniformly mixed together to obtain a colorless and clear elixir preparation. A five-milliliter dosage of this elixir preparation contains 50 mg of phytic acid.

Production Example 2 (Capsules)

Composition A	200 mg	(40 mg calculated as phytic acid)
Lactose	20 mg	
Corn starch	38 mg	
Magnesium stearate	2 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together and packed in No. 2 capsules. One such capsule contains 40 mg of phytic acid.

Production Example 3 (Granules)

Composition A	600 mg	(120 mg calculated as phytic acid)
Lactose	140 mg	
Corn starch	250 mg	
Hydroxypropylcellulose	10 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then wet-granulated with water and ethanol into granules. One hundred and twenty (120) mg of phytic acid are contained in an one-gram dosage of such granules.

Production Example 4 (Powder)

The composition A is divided and heat-sealed in aluminium to obtain wrappers each of 1.5 g of powder.

Production Example 5 (Tablets)

Composition A	100 mg	(20 mg calculated as phytic acid)
Corn starch	19 mg	
Crystalline cellulose	30 mg	
Magnesium stearate	1 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then compressed into tablets each of 7 mm in diameter and 150 mg in weight. One such tablet contains 20 mg of phytic acid.

Production Example 6 (Syrup)

Composition C	50 g	(5 g calculated as phytic acid)
White sugar	300 g	
D-sorbitol (70%)	250 g	
Methyl p-oxybenzoate	0.3 g	
Propyl p-oxybenzoate	0.15 g	
Sodium citrate	10 g	
Perfume	1.5 g	
Refined water	Total: 1000 ml	

Predetermined amounts of the aforesaid components are dissolved and mixed together into a colorless and clear syrup. One hundred (100) mg of phytic acid is contained in a twenty-milliliter dosage of this syrup.

Production Example 7 (Dry syrup)

Composition B	100 mg	(10 mg calculated as phytic acid)
Sodium citrate	2.4 mg	
Citric anhydride	2.2 mg	
Tragacanth powders	2.7 g	
White sugar	suitable amount	
Hydroxypropylcellulose	3.0 mg	
Perfume	slight amount	
Perfume	slight amount	

Predetermined amounts of the aforesaid components are uniformly mixed together, and are then wet-granulated with water and ethanol into a dry syrup. An one (1)-gram dosage of this syrup contains 10 mg of phytic acid.

Production Example 8 (Troche)

Composition A	100 mg	(20 mg calculated as phytic acid)
White sugar	870 mg	
Lactose	20 mg	
Magnesium stearate	10 mg	

Of the aforesaid components the composition A and white sugar are uniformly mixed together in the respective amounts of 100 g and 870 g, and are then wet-granulated with water and ethanol, followed by drying at a temperature of lower than 35°C. Added to the dried product are 20 g of lactose and 10 g of magnesium stearate to obtain troches each of 15 mm in diameter and 1 g in weight. One such troche contains 20 mg of phytic acid.

Production Example 9 (Candy)

Composition B	100 mg	(10 mg calcuated as phytic acid)
White sugar	2400 mg	
Starch syrup	1500 mg	
Perfume	slight amount	

Of the aforesaid components, 240 g of white sugar and 150 g of starch syrup are mixed with 100 g of refined water. After melting by heating, the mixture is sieved for the removal of foreign matters. The resulting liquid is concentrated under pressure with the application of heat for dehydration to prepare a starch syrup dough having a moisture content of 2 to 3 % at 130 to 150°C. Added to this dough are 10 g of the composition B and a slight amount of perfume, and the product is molded to obtain candies each of 4 g in weight. Each candy contains 10 mg of phytic acid.

EMI ID=11/3 HE=10 WI=145 TI=TAB

EMI ID=12/1 HE=25 WI=145 TI=TAB

Predetermined amounts of the aforesaid components are uniformly mixed together into "limonada". A thirty (30)-milliliter dosage of such limonada contains 300 mg of phytic acid.

Production Example 11 (Granule)

Composition D	500 mg	(100 mg calculated as phytic acid)
Garlic Powders	750 mg	
Lactose	suitable amount	

Predetermined amounts of the aforesaid components are uniformly mixed together, and are then wet-granulated with water and ethanol into granules. One hundred (100) mg of phytic acid is contained in an 1.5-gram dosage of such granules.

Production Example 12 (Drinkable Solution)

Composition C	1 g	(100 mg calculated as phytic acid)
Mel	0.5 g	
White sugar	2.0 g	
Citric acid	suitable amount	
Sodium citrate	suitable amount	
Peppermint	slight amount	
Refined water	suitable amount	

Predetermined amounts of the aforesaid components were uniformly mixed together into a colorless and clear internal liquid preparation. A thirty (30)-milliliter dosage of this liquid preparation contains 100 mg of phytic acid.

Production Example 13 (Garlic Flavoring)

Composition D	0.285 g	(0.1 g calculated as phytic acid)
Avisel	0.18 g	
Garlic powders	0.75 g	
Light silicic anhydride	0.256 g	
Corn starch	suitable amounts	

Predetermined amounts of the aforesaid components are granulated by a conventional method.

Stability Testing

The preparations according to Production Examples 1 to 10 were subjected to stability testing to measure the amount of residual phytic acid. The results are set forth in Table 2.

Table 2

Amounts of Residual Phytic Acid in the Stability Testing of the Preparations According to the Production Examples (% with respect to the specified contents)

Samples	Storage Vessels	At the beginning of Storage	After 3 weeks at 60°C
P.Ex.1A*	Glass Bottle	100.5	101.2
P.Ex.2B*	PTP	101.4	99.4
P.Ex.3C*	Aluminium Wrapper	100.1	100.0
P.Ex.4D*	"	100.9	102.1
P.Ex.5E*	PTP	99.2	99.8
P.Ex.6F*	Glass Bottle	102.1	100.3
P.Ex.7G*	Aluminium Wrapper	100.6	100.1
P.Ex.8H*	Aluminium SP	99.7	100.5
P.Ex.9I*	Aluminium Bag	99.9	99.2
P.Ex.10J*	Glass Bottle	102.1	100.9
P.Ex.11K*	Aluminium Wrapper	100.3	100.1
P.Ex.12L*	Glass Bottle	100.1	99.8

A*: Elixir,
B*: Capsule,
C*: Granule,
D*: Powder,
E*: Tablet,
F*: Syrup,
G*: Dry Syrup,
H*: Troche,
I*: Candy,
J*: Limonada,
K*: Granule,
L*: Drinkable Solution.

Pharmaceutical Effect Test 1 (Induction of Lipoprotein Lipase (LPL for short)

(a)Test Animals and Procedures

In a range of 1 to 50 mg, sodium phytate was administered under anasthesia to four groups of Wistar rats each weighing 190 to 200 g and previously fasted for 12 hours or longer. Five minutes after the administration, blood was gathered from the descending aorta. Sodium citrate was added to the collected blood to regulate its final concentration to 3 mg/ml, which was in turn centrifuged to obtain plasma.

(b)Test Procedures

The activity of LPL in the obtained plasma was determined by the measurement of liberating fatty acids. The free fatty acids were measured with NEFAC Test Wako-Kit (by Wako Junyaku Co., Ltd.).

(c)Test Results

1) The results of changes in the free fatty acids with changes in the dosage are shown in Figure 1.

By measurement, it has been found that the free fatty acids are induced depending upon the amount of sodium phytate in the range of 1 to 50 mg/kg/weight, but the animals are killed with a dosage exceeding 50

mg/kg/weight.

2) Results of Induction-with-time of Free Fatty Acids

With an intravenous injection of sodium phytate in an dosage of 20 mg/kg/weight, the maximum induction of LPL occurred five minutes after the injection, and was sustained over about 40 minutes, as can be seen from the results shown in Figure 2.

From the foregoing results, it has been found that the present compositions are effective in lowering lipid levels.

Pharmaceutical Effect Test 2 (Weight Reductions)

50, 100 and 150 mg/kg of sodium phytate were intraperitoneally administered to test groups of 13 or 14 mice weighing about 26 g, once a day for 6 days, and physiological saline alone was administered to a control group of 11 mice of the same weight.

The results, as shown in Table 3, have indicated that there are reductions in the weight and such reductions are noticeable in a dosage of 150 mg/kg.

Table 3

Reductions in the Weight of Mice

	Dosage (mg/kg i.p.)	Number of Mice	Weight		
			Day of Administration	1st Day	6th Day
Control Group		11	26.7±0.5	27.5±0.5	29.8±0.6
Test Groups	50	14	26.2±0.4	26.7±0.4	29.1±0.4
	100	14	26.1±0.3	26.3±0.4	28.7±0.4
	150	13	26.1±0.4	26.0±0.4	27.6±0.4

Pharmaceutical Effect Test 3 - (Inhibition of Propagation of Fat Cells of Mice)

Skin cells of a mouse just after birth were collected after decapitation, and a culture liquid was added thereto for 2-day cultivation in a Schale (a laboratory dish). On the third day, an additional culture liquid was provided and, at the same time, sodium phytate was added to a test group at a concentration of 100 ug/ml to observe under a microscope changes in the skin and fat cells on a daily base from the third day after incubation.

From the results, it has been found that the fat cells of the control group show an increase in the amount of fat, but the fat cells of the test group tend to show a decrease in the amount of fat. In both the test and control groups, no change in the skin cells is found, which means that the toxicity of sodium phytate makes no contribution to the reduction in the fat cells.

Organoleptic Tests

Organoleptic: Comparison Test 1

For organoleptic comparison testing on whether the taste, edibility and the smell are good or bad, beefsteaks cooked with 0.5 g (33 mg calculated as phytic acid) of the garlic flavoring preparation according to Production Example 13 and other seasonings were fed to a 20-member panel simultaneously with those without phytic acid. The results are shown in Table 4.

Table 4

	Indistinguishable from phytic acid-free steaks	Better than phytic acid-free steaks	Bad
Taste	6	14	0
Edibility	5	15	0
Smell	1	19	0

From the above results, it has been found that phytic acid excels in taste, edibility and smell, and is effective as a food flavoring material.

Organoleptic Test 2

Thirty (30) ml (100 mg calculated as phytic acid) of the drinkable solution of Production Example 12 was continuously administered to three patients suffering from diabetic hyperlipemia once a day for 7 days, and a questionnaire was conducted on its drinkability and effects. The results are shown in Table 5.

Table 5

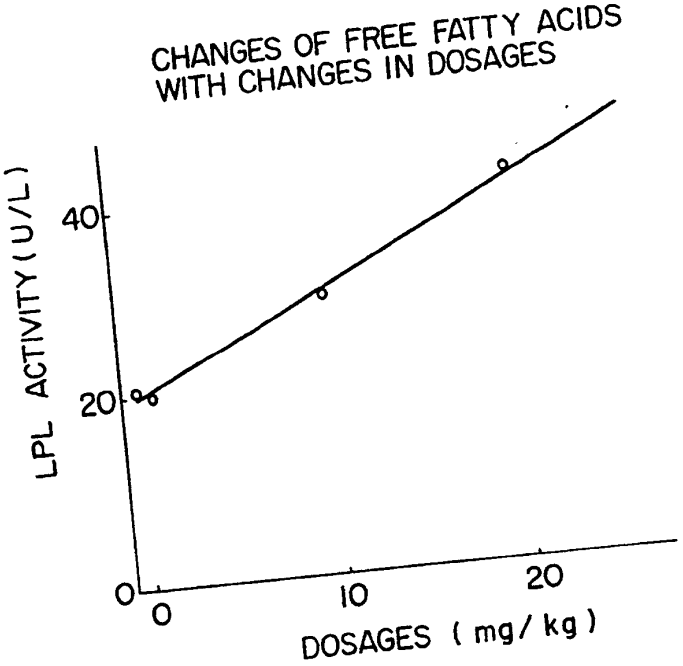
		Good	Indistinguishiable
Drinkability		3	0
Effects	(a) Recovery from fatigue	2	1
	(b) Amelioration of conditions	3	0

It is here to be noted that this drinkable solution was administered to the patients, while suggesting that it was a healthy diet effective for diabetes. Although it may not be possible to deduce from such results any significant comment on the mechanism of action of phytic acid, it is believed that phytic acid is organoleptically effective as a food additive.

Claims

1. Use of phytic acid and/or a salt thereof for the manufacture of a medicament for treating or preventing hyperlipemia.
2. Use of phytic acid and/or a salt thereof for treating or preventing obesity and obesity-related diseases.
3. Use as claimed in Claim 2, wherein the obesity-related diseases are fat liver, diabetes and macromastia.
4. Use as claimed in any preceding claim wherein the salt of phytic acid is a non-toxic metal salt or a non-toxic salt with an organic base, a basic amino acid or an organic ester residue.
5. Use as claimed in Claim 4, wherein the salt of phytic acid is an iron salt.
6. Use as claimed in Claim 4, wherein the salt of phytic acid is selected from potassium phytate, sodium phytate, ammonium phytate, arginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamine phytate, diethanoamine phytate, triethanolamine phytate and glucamine phytate.
7. Use as claimed in any preceding claim, in a dosage of 1 to 100 mg per kg body weight per day and in a form suitable for oral administration.
8. Use as claimed in any preceding claim, wherein the phytic acid or salt is included in a food or a drink.

FIG. 1


CHANGES OF FREE FATTY ACIDS
WITH CHANGES IN DOSAGES
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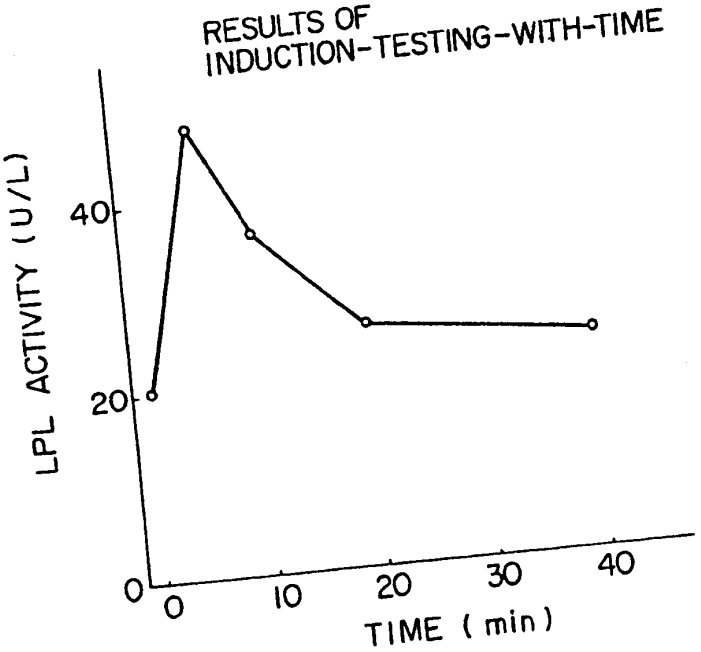
20
0
0
10
20
DOSAGES (mg/ kg)

FIG. 2


RESULTS OF
INDUCTION-TESTING-WITH-TIME
LPL ACTIVITY (U/L)
40
20
0
0
10
20
30
40
TIME (min)

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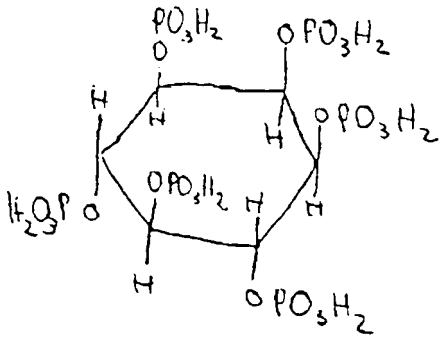

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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	NUTR. REP. INT., vol. 15, no. 5, May 1977, pages 587-595; L.M. KLEVAY: "Hypocholesterolemia due to sodium phytate" * Page 590, figure 1; page 591, lines 30-33; page 592, lines 26-29 * ---	1,4-8	A 61 K 31/66
X	AM. J. CLIN. NUTR., vol. 28, no. 4, 1975, page 426; L.M. KLEVAY et al.: "Zinc/copper hypercholesterolemia: The effect of sodium phytate" * Page 426, lines 14-27 * ---	1,4-8	
X	67TH ANNUAL MEETING OF THE FEDERATION OF AM. SOC. EXP. BIOL., Chicago, 10th - 15th April 1983, Fed. Proc. 1983, vol. 42, no. 5, abstract no. 5230; M.A. BOCK et al.: "Lipid metabolism: Interaction effects of dietary pectin, phytate, and calcium with zing and copper" * Abstract * ---	1,4-8	
Y	AM. J. CLIN. NUTR., vol. 46, no. 3, 1987, pages 467-473, Am. Society for Clinical Nutrition, US; L.U. THOMPSON et al.: "Phytic acid and calcium affect the in vitro rate of navy bean starch digestion and blood glucose response in humans1-3" * Page 467, left-hand column, lines 1-2,14-19; page 469, figure 3; page 470, figure 5; page 471, left-hand column, lines 3-9, right-hand column, lines 3-5,33-41; page 472, left-hand column, lines 17-32 * -/- ---	1,4-8	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-01-1991	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

x LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

1. Claims 1; 4-8 (partially): Use of the claimed compounds for the preparation of a medicament for treatment of hyperlipidemia
2. Claims 2,3; 4-8 (partially): Obesity and "related diseases"

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims:

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 4985

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	AM. J. CLIN. NUTR., vol. 42, October 1985, pages 604-617, Am. Society for Clinical Nutrition, US; D.J.A. JENKINS et al.: "Low glycemic index carbohydrate foods in the management of hyperlipidemia[1-3]" * Page 609, right-hand column, lines 32-42; page 612, left-hand column, lines 11-16 * ---	1,4-8	
A	BIOCHIM. BIOPHYS. ACTA, vol. 360, 1974, pages 134-145, Elsevier Scientific Publishing Co., Amsterdam, NL; E. HAYASHI et al.: "The effect of myo-inositol deficiency on lipid metabolism in rats" * Page 140, line 26 - page 141, line 5; page 143, lines 41-48 * ---	1,4-8	
A	"The Merck Manual", 15th edition, Robert Berkow, Ed., pages 951-955, Merck Sharp & Dohme Research Laboratories, Rahway, NJ, US * The whole document * ---	1-8	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	THE AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 38, September 1983, pages 481-488, American Society for Clinical Nutrition, US; M.J. THORNE et al.: "Factors affecting starch digestibility and the glycemic response with special reference to legumes[1-3]" * Page 483, left-hand column, lines 22-27 * --- -/-	2-3	

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X	JOURNAL OF FOOD SCIENCE, vol. 49, 1984, pages 1228-1229; L.U. THOMPSON et al.: "Starch digestibility as affected by polyphenols and phytic acid" * Page 1228, left-hand column, lines 15-23, right-hand column, lines 6-11,40-42 * ---	2-3	
X	191ST AMERICAN CHEMICAL SOCIETY NATIONAL MEETING, New York, 13th - 18th April 1986, abstr. PAP. AM. CHEM. SOC., vol. 191, no. 0, 1986, no pagination, abstract no. 51; L.U. THOMPSON: "Influence of phytic acid on starch digestibility and blood glucose response" ---	2-3	
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Y	THE JOURNAL OF VITAMINOLOGY, vol. 17, 1971, pages 112-116; I. NISHIGAKI et al.: "Studies on myoinositol. VII. Removal of deposited fats from dietary fatty liver" * Page 112, left-hand column, lines 8-14; page 114, left-hand column, lines 13-25; page 116, left-hand column, lines 27-29 * ---	2-3	

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Y	THE JOURNAL OF VITAMINOLOGY, vol. 16, no. 1, 1970, pages 75-79; A. KOTAKI et al.: "Studies on myoinositol. V. Effect of myoinositol on the prevention of fatty liver induced by orotic acid" * Page 75, left-hand column, lines 1-10; page 78, left-hand column, lines 10-13 *	2-3	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

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